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Radiation Therapy for Extrapelvic Lymph Node Recurrence After Curative Treatment for Cervical Cancer

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Abstract. *Background/Aim: To investigate outcomes of patients with cervical cancer who received radiation therapy for extrapelvic lymph node recurrence after initial pelvic radiotherapy. Patients and Methods: The treatment charts of 20 patients were retrospectively reviewed, and factors influencing patient's prognosis were statistically analyzed. Results: The three-year in-field tumor control rate was 55% and overall survival (OS) at 2, 3, and 5 years was 55%, 45%, and 37.5%, respectively. The rate of the three-year OS in patients with recurrence within and after 9 months was 20% and 70%, respectively (p=0.016). None of the 4 patients who were diagnosed with supraclavicular lymph node recurrence alone at more than 9 months after initial treatment experienced further recurrence. Five-year survival of the remaining 16 patients was only 21% (p=0.021). Conclusion: Time to recurrence significantly influenced survival in patients with cervical cancer who received radiotherapy for extra-pelvic lymph node recurrence. Supraclavicular lymph node recurrence alone had a favorable impact on patient's prognosis.*

Lymph node recurrence outside the initial radiation field is sometimes encountered during the follow-up period after curative treatment in patients with cervical cancer (1-4). Frequently observed sites of lymph node recurrence include the para-aortic lymph nodes (PAN), supraclavicular lymph nodes (SCLN), and mediastinal lymph nodes (MLN). PAN metastases alone following radiation therapy has been previously reported (5-7). These studies have shown that factors such as diagnosis without any symptom, irradiation dose ≥50 Gy and blood serum squamous cell carcinoma antigen levels ≤10 ng/ml are related to a favorable prognosis. Although these sites are beyond the "local-regional" area of cervical cancer, aggressive radiation therapy is often administered for PAN, SCLN, and MLN recurrences with the aim of achieving not only palliative effects, but also control of recurrent lymph nodes and subsequent survival prolongation (8, 9). In the present study, outcomes of radiation therapy with or without concurrent chemotherapy in patients with lymph node recurrence after the initial curative pelvic treatment were investigated. Factors that might influence control of lymph node recurrence and patient survival were also assessed.

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Key Words: Lymph node recurrence, radiation therapy, cervical cancer.

Materials and Methods

Between September 2002 and February 2015, 327 patients with cervical cancer received radiation therapy as an initial treatment at Chiba University Hospital, Chiba, Japan. Of those, 20 patients had lymph node recurrence as the first failure site outside the initial radiation field, and received radiation therapy thereafter. The patients' characteristics are shown in Table I. The median age was 54 years (range=29-75 years). Performance status (PS) according to the Eastern Cooperative Oncology Group was 0 or 1. The median interval between the end of the initial treatment and the diagnosis of lymph node recurrence was 10 months, with a range of 1 to 50 months. Eight patients had SCLN recurrence alone, 7 patients had PAN recurrence alone, 1 had MLN recurrence alone, 2 had simultaneous SCLN and PAN recurrences, and 2 had SCLN and MLN recurrences. Diagnosis of lymph node recurrence was clinically established using both physical and radiological examination techniques; the latter included computed tomography (CT), ^{18}F-fluorodeoxyglucose positron emission tomography (PET), and PET-CT. Histopathological or cytological confirmation was performed for SCLN recurrence. No patients had other visceral metastasis. Initial treatments performed prior to lymph node recurrence are summarized in Table I. Clinical factors at initial treatment were as follows; 4 cases were stage IB, 7 were stage II, and 9 were stage IIIB according to the International Federation of

Table I. *Patient characteristics*.

No.	Age at rec.	Site of rec.	Time to rec. (mo)	EBRT EQD2 (Gy)	Chemotherapy	Clinical factors at initial treatment				
						FIGO stage	Histologic type	RT field	EBRT (Gy)	Brachytherapy
1	54	SCLN	18	49	–	IIA**	adeno	WP+PAN	50.4	–
2	55	SCLN	8	55	–	IIIB	SCC	WP+PAN	54	–
3	37	SCLN	6	44	+	IIIB	adeno	WP+PAN	55	–
4	58	SCLN	38	50	+	IB2	adeno	WP+PAN	50.4	+
5	54	SCLN	7	50	–	IIIB	SCC	WP+PAN	56	+
6	36	SCLN	4	54	+*	IIB	AdQ	WP+PAN	50	+
7	64	SCLN	17	56	+	IIB	SCC	WP+PAN	54	+
8	64	SCLN	10	47	–	IVB	SCC	WP+PAN	45	+
9	54	PAN	1	40	–	IIIB	adeno	WP	50.4	+
10	60	PAN	24	50	–	IIB**	adeno	WP	50	–
11	54	PAN	11	40	+	IIIB	SCC	WP	50	+
12	29	PAN	6	50	+	IB2	adeno	WP	50	+
13	38	PAN	4	40	+	IIIB	SCC	WP	50	+
14	43	PAN	6	54	+	IIIB	SCC	WP	60	+
15	41	PAN	50	50	+	IB1**	SCC	WP	58	–
16	36	SCLN/MLN	5	60	+	IIB	SCC	WP+PAN	50	+
17	40	SCLN/MLN	28	50	+	IIB	SCC	WP+PAN	50	+
18	59	SCLN/PAN	6	39	–	IIB	SCC	WP	50	+
19	75	SCLN/PAN	35	58, 48	+	IB1**	SCC	WP	59.4	–
20	69	MLN	14	60	+	IIIB	adeno	WP+PAN	50	+

mo: Months; SCLN: supraclavicular lymph node; PAN: para-aortic lymph node; MLN: mediastinal lymph node; EQD2: equivalent dose in 2 Gy fractions; adeno, adenocarcinoma; SCC: squamous carcinoma; AdQ: adenosquamous carcinoma; WP: whole pelvis; *daily cisplatin + weekly paclitaxel; **postoperative irradiation for vaginal stump recurrence or adjuvant therapy.

Gynecology and Obstetrics (FIGO) staging classification. Sixteen patients received definitive radiation therapy and 4 received radical hysterectomy followed by adjuvant radiation therapy. Nineteen patients received concurrent chemoradiotherapy by administering daily a low-dose of 8 mg/m^2 cisplatin (10). For 1 of these 19 patients, paclitaxel (50 mg/m^2) was weekly added as a specific regimen for adenosquamous carcinoma. The remaining 1 patient was treated with radiation therapy alone. As for the field of initial radiotherapy, extended-field radiation therapy covering the PAN area was used for 11 patients and whole-pelvic radiotherapy for 9 patients. All patients, including 3 patients who had undergone adjuvant hysterectomy after chemoradiation, achieved local-regional control after the initial treatment.

This retrospective study was approved by the Institutional Review Board of our hospital (No. 2925) and performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all patients.

Treatment of lymph node metastasis

Radiation therapy. All patients were treated with high-energy X-ray using a linear accelerator. CT-based 3-dimensional treatment planning was performed for all patients. Because of the retrospective nature of this study, therapeutic parameters such as total dose, dose per fractionation, and clinical target volume (CTV) of radiation therapy were individualized and varied from patient to patient, considering each patient's clinical factors such as site of recurrence, distribution and numbers of recurrent lymph nodes, size of lymph nodes, and use of concurrent chemotherapy, as well as socio-economic factors. For all patients, the gross tumor volume was determined on CT images. For 19 patients with SCLN or PAN recurrence, the involved lymph node area as a whole was set as the CTV, taking care not to overlap the initial treatment field for patients with PAN recurrence. For 1 patient with a solitary enlarged node at the mediastinum, the swollen node with generous margins was defined as the CTV. The total dose of radiation therapy ranged from 36 to 56 Gy, with a median of 50 Gy, delivered using 5 daily fractionations of 2.0 to 3.0 Gy. For 13 patients who underwent concurrent chemotherapy, the fractional daily dose was fixed at 2.0 Gy. Because of the use of different fractionation schedules for individual patients, the total dose was calculated as the equivalent dose in 2-Gy fractions (EQD2) for each patient by using alpha/beta=10 Gy (11). The median EQD2 was 50 Gy, with a range of 39 to 60 Gy.

Chemotherapy. The application of concurrent chemotherapy for individual patients was clinically determined by both gynecological oncologists and radiation oncologists by taking into account the patient's performance status at recurrence. Thirteen patients received concurrent chemoradiotherapy by administering daily a low-dose of 8 mg/m^2 cisplatin . Radiation monotherapy was administered to the remaining 7 patients.

Follow-up and toxicity/response assessment. During the treatment, patients were examined every week by both gynecologic oncologists and radiation oncologists. After the treatment for lymph node metastases, patients were followed up once per month for the first year and once every 3 months thereafter. Radiological examination

Table II. *The response and patterns of failure of patients.*

No.	Response*	Recurrence type	Follow-up (month)	Status
1	CR	-	154	NED
2	CR	Marginal	22	DOD
3	CR	-	130	NED
4	CR	-	92	NED
5	CR	In	22	DOD
6	PR	In/out	11	DOD
7	CR	-	41	NED
8	CR	-	122	NED
9	PD	(Progression)	6	DOD
10	NC	In	5	DOD
11	NC	In/out	11	DOD
12	PR	In/out	35	DOD
13	CR	In	53	DOD
14	PR	In	11	DOD
15	CR	-	60	NED
16	CR	Marginal	9	DOD
17	CR	In	44	AWD
18	PR	In	16	DOD
19	CR	-	37	NED
20	CR	Marginal	29	DOD

*Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1. Marginal: Marginal recurrence; in: in-field recurrence; out: out-of-field recurrence; NED: no evidence of disease; AWD: alive with disease; DOD: died of disease.

such as CT was also performed if clinically indicated. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4). Responses to treatment were assessed using physical examination and CT, and classified according to the Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1.

Statistical analyses. Overall survival was estimated using the Kaplan–Meier method. Statistical significance was tested by log-rank test. Effects of factors such as age, use of chemotherapy, dose of radiotherapy in EQD2, histopathological diagnosis, site of recurrent nodes and time interval between initial treatment and diagnosis of nodal recurrence on patient prognosis were examined. All statistical analyses were performed with PASW Statistics 18 (SPSS Inc. Chicago, IL, USA).

Results

There was no Grade 4 or worse acute adverse event. Grade 2 or worse acute adverse events included pharyngitis in 1 patient, leukopenia in 9 patients, thrombocytopenia in 7 patients, and dermatitis in 1 patient. Response to treatment, type of recurrence, follow-up period and status of all patients are shown in Table II. Complete response was obtained in 13 patients (65%), partial response in 4 (20%), no change in 2, and disease progression in 1, resulting in a response rate of 85%. During the follow-up period, 13 patients, including 1 patient with disease progression, experienced recurrence. In-field recurrence was observed in 6, marginal recurrence in 3, and both in-field and out-of-field recurrence in 3 patients. The three-year in-field tumor control rate was 55%. At the time of data analyses, 7 patients still showed no evidence of disease (NED). Overall survival at 2, 3, and 5 year was 55%, 45%, and 37.5%, respectively, with a median follow-up time of 35 months (range=5-154 months) (Figure 1). The median survival time after treatment for lymph node recurrence was 29 months. Time between initial radiation therapy and lymph node recurrence had significant impact on subsequent patient's survival. The three-year overall survival in patients with recurrence within and after 9 months was 20% and 70%, respectively (p=0.016, Figure 2). Patients with NED at the time of the data analyses had a significantly longer time to recurrence value than the remaining patients. The mean time to recurrence after initial treatment was 24.9 months (range=6-50 months) for 7 patients with NED as compared with 9.9 months (range=1-29 months) for the remaining 13 patients (p=0.017, Mann-Whitney U-test). Patterns of recurrence had marginal impact on patient's prognosis. The three-year overall survival in patients with SCLN recurrence alone and those with other lymph node recurrence sites was 63% and 33%, respectively (p=0.086), and in patients with and without PAN recurrence was 33% and 55%, respectively (p=0.14). None of the 4 patients who had SCLN recurrence alone more than 9 months after the initial radiation therapy experienced further recurrence. These 4 patients are still maintaining NED status with a respective follow-up period of 41, 92, 122 and 154 months. Total dose in EQD2 for these 4 patients ranged from 48 to 56 Gy. The five-year survival of the other 16 patients was only 21% (p=0.021, Figure 3).

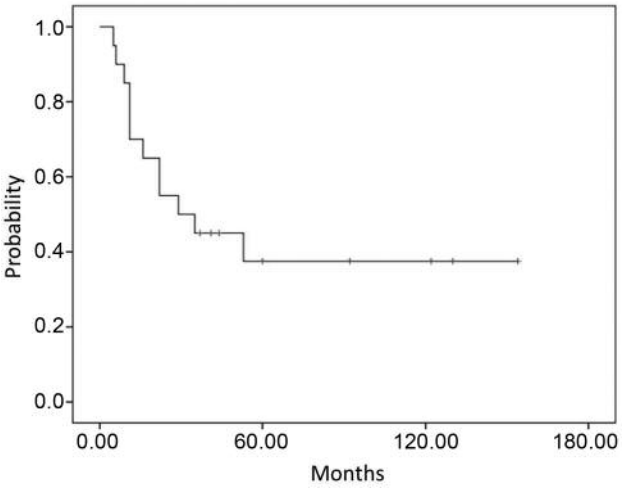

Figure 1. *Kaplan–Meier overall survival curve of all patients.*

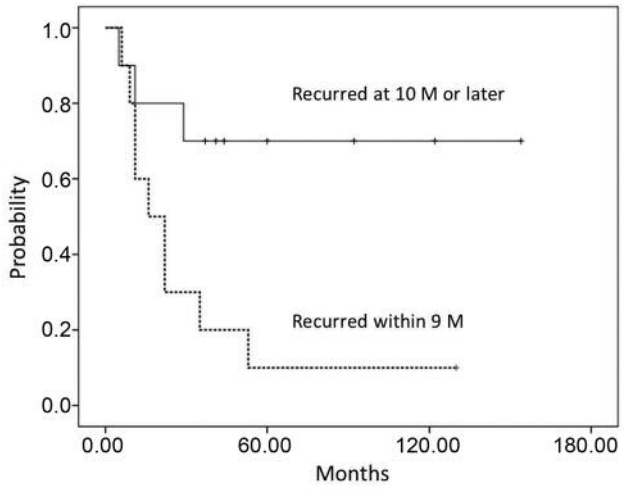

Figure 2. *Overall survival of patients after radiation therapy for lymph node recurrence occurring within 9 months or later.*

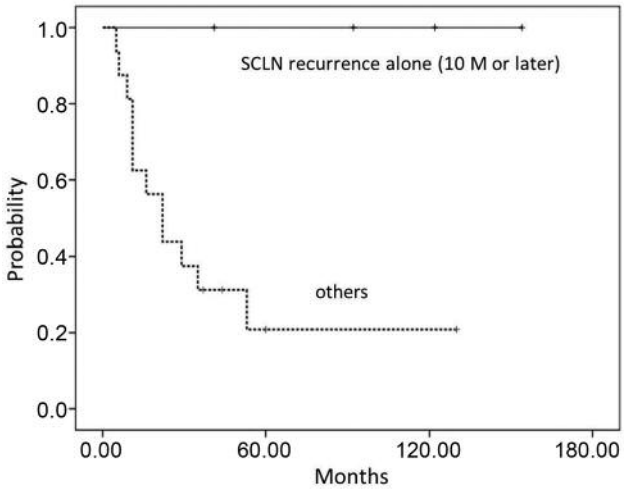

Figure 3. *Overall survival, in 4 patients who had supraclavicular lymph node recurrence alone more than 9 months after initial radiation therapy, and in the remaining 16 patients.*

No other clinical factors such as age, use of chemotherapy, dose of radiotherapy in EQD2, and histopathological diagnosis influenced patient's prognosis. Although the 5-year survival rate for 13 patients who received concurrent cisplatin was higher than that for the remaining 7 patients, this difference was not significant (50% *vs.* 33%, p=0.71).

Discussion

Extra-pelvic lymph node recurrence is sometimes encountered during the follow-up period after curative treatment in patients with cervical cancer. Chou *et al.* retrospectively analyzed 26 patients with isolated PAN recurrence after curative radiation therapy (7). Patients with asymptomatic recurrence were more often treated with salvage cisplatin-based chemoradiation, and showed significantly higher overall survival rate as compared with those with symptomatic recurrence (50% *vs.* 0% at 5 years, p=0.0135). Among 84 patients with PAN recurrence, including 26 patients after surgery, Niibe *et al.* also reported significantly higher overall survival for those without symptoms (6). Singh *et al.* similarly reported a good prognosis for those with asymptomatic PAN recurrence after pelvic radiation therapy (5). They showed that the 5-year overall survival after salvage treatment was significantly higher for patients with a time to recurrence of >24 months than those within 24 months (80% *vs.* 14%, p=0.0067). As for isolated PAN recurrence, Grigsby *et al.* also showed that the median survival was related to the disease-free interval, 7.5 months for the patients who failed within 2 years *vs.* 17.8 months for those who failed later (12). In the present study, time between initial radiation therapy and lymph node recurrence had significant impact on subsequent patient's survival. Patients with NED at the time of the data analyses had a significantly greater time to recurrence than the remaining patients. The patterns of recurrence had marginal impact on survival. Patients with SCLN recurrence alone had relatively favorable prognosis. On the other hand, patients with PAN recurrence had lower 3-year survival than those without PAN recurrence. It was considered that this may be due partly to the difficulty in the treatment planning for PAN recurrence because of overlap with initial treatment field. Extremely good prognosis in patients with SCLN recurrence alone which occurred at a longer period from the initial treatment could be another reason. There exist some limitations in this study, such as the small and heterogenic patient groups. However, the results demonstrated that a favorable prognosis could be expected for patients with SCLN recurrence alone after a relatively long latent period. Time between initial radiation therapy and recurrence as well as site and patterns of recurrence should be well taken into account when physicians plan to treat cervical cancer patients who suffered nodal recurrence.

Conclusion

For some patients with lymph node recurrence outside the initial radiation field, favorable prognosis can be expected by radiation therapy.

Authors' Contributions

The Authors contributed equally to this study's design and data interpretation. The corresponding Author and A.K. had full access

to all data in the study and had a responsibility for manuscript drafting or manuscript revision for important intellectual content. The Authors approved the final version of the submitted manuscript.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

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